REMARKS

On November 9, 2004 Applicants' undersigned attorney conducted an interview with SPE Gary Kunz. The Examiner is thanked for the courtesies extended during the course of the interview.

During the interview, undersigned counsel detailed why the Depui reference does not contain disclosure so as to enable one of ordinary skill to provide a formulation wherein the dosage form is stabilized in the absence of a separating layer. Attention was invited to the comparative data set forth in Example 1, Tables 1 to 3 of the Lovgren '505 patent. This data shows that prior art formulations not containing a separating layer, but containing an active ingredient within the scope of that recited in the now pending claims, showed a rapid degradation. Example 1 of Lovgren '505 contains no disclosure as to whether the active ingredient was in the form of an active layer, as recited in the now pending claims, or was in a core formed by an extrusion process wherein the active ingredient and all the core excipients were intermixed. Since Example 1 of the '505 patent refers to tablets, one may well conclude that the active ingredient is within the core rather than in a drug containing layer.

Applicants also expressed concern as to the manner in which the previously submitted Molina declaration was addressed. Because of the lack of detail or exemplification of any embodiment of a dosage form without a separating layer in the Depui reference, Applicants had attempted a form of comparison to other prior art which contained more detail and which dealt with these types of compounds. Examiner was again referred to the differences in stability. Even though the declaration was submitted many months ago, the Examiner has yet to substantively address that declaration.

Turning to the Office Action of June 1, 2004, claims 1 to 13, 26 to 29, 37 and 38 were rejected under 35 U.S.C. 102(e) as anticipated by U.S. Patent No. 6,132,771 to Depui et al. ("Depui"). It is submitted this rejection is in error as a matter of law and should be withdrawn.

For a reference to anticipate a claimed invention, that single reference must show each and every feature of the claimed invention arranged as in the claim. See *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q.

193 (Fed. Cir. 1993). That reference must contain sufficient disclosure as to convince one of ordinary skill in the art that the inventor had possession of the invention at the time the reference was filed. When a composition is claimed, an anticipating reference must completely identify the claimed composition, as it is set forth in the claim, and must also provide an enabling disclosure so that one of ordinary skill in the art can, without undue experimentation, make the invention. See *In re Sheppard* 144 U.S.P.Q. 42 (CCPA 1964). If a reference fails to properly identity the invention or to enable one to make the invention without undue experimentation, that reference does not describe the invention and cannot be an anticipatory reference.

It is submitted that the Depui reference does not anticipate the now claimed invention as a matter of law. It neither identifies the claimed invention, nor does it enable one of ordinary skill in the art to make the invention without undue experimentation.

The Depui patent, assigned to Astra-Zeneca, is directed to an oral pharmaceutical dosage form for a combined therapy against GORD (Gastro Oesophageal Reflux Disease). The dosage form is preferably a tablet containing an acid suppressing agent (proton pump inhibitors i.e. omeprazol, lansoprazol,...) and a prokinetic agent (i.e. cisapride, mosapride,...).

A. Depui Fails to Identify the Claimed Invention

Depui never discloses or suggests that the active containing layer is substantially non-porous. See line 3 of pending claim 1. Importantly, the rejection does not state, or suggest, that the reference shows or suggests this feature of the now claimed invention.

All 14 examples of Depui refer to a proton pump inhibitor dosage form having an alkaline substance and at least one separating layer between the core and the surrounding enteric coating. The alkaline substance can be included as a basic salt of the corresponding proton pump inhibitor, i.e. omeprazole magnesium salt, as stated in the '505 (col. 4, lines 23 to 27) and '230 (col. 8, lines 55 to 61) patents. The references examples merely refer to the active layer being applied to the seed. There is not a single example, suggestion,

description or mention of a stable and useful composition or composition with a substantially non-porous active layer as defined in the presently pending claims. Accordingly, Depui fails to identify the invention as claimed and thus the anticipation rejection is in error as a matter of law.

B. Depui Fails to Enable the Claimed Invention

In column 2, starting at line 47, Depui describes as obvious that the proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer and specifically refers to U.S. Patent No. 4,786,505 ("the 505 patent") for omeprazole preparations (see col. 2, lines 50-57) with a description of enteric coating layered preparations of proton pump inhibitors.

The '505 patent discloses omeprazole pellets having a core containing omeprazole and an alkaline substance, one or more separating layers, and an outer enteric coating. The separating layer(s) are described as necessary because: *"The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discoloration of omeprazole during the coating process or during storage."*(see '505 col. 3, lines 4-8). U.S. Patent No. 4,853,230 (the '230 patent), contains similar disclosure relating to other proton pump inhibitors (see col. 8, line 67 to col. 9, line 4).

Both the '505 (col. 3, lines 36 to 65) and the '230 (col. 8, lines 31 to 61) patents refer to the importance of the presence of an alkaline substance and both contain extensive disclosure as to the necessity of the separating layer because of the acid sensitivity of omeprazole and other so called acid labile compounds and the negative experiences in bio-studies of compositions without the separating layer. The '505 patent refers to an article "Development of an Oral Formulation of Omeprazole", Scand. J. Gastroenterology, 1985, pgs. 113-120 describing conventional enteric coated dosage forms and their stabilization. The '505 patent also contains an example (Example 1) comparing the stability of tablets with and without separation layers. According to the '505 patent, those dosage forms without the separating layer showed poor and unacceptable stability.

Depui fails to describe how a stable and useful oral dosage form of a proton pump inhibitor can be made without having both an alkaline reacting substance and at least one separating layer. That is to say, even if Depui contained sufficient disclosure to identify the now claimed composition, Depui fails to contain enabling disclosure as to how to make such a composition.

The Examiner has referred to text in the reference calling the separating layers(s) "optional". However, that "optional" feature is referred to only generally and it is not supported by the cited prior art or by the patent description. Since the main object of Depui is a combined therapy for GORD, the patentee sought broad protection and attempted to foreclose others from patenting a composition with no separating layer by a non-informative characterization of such a feature as "optional". However, Depui fails to even hint at how a useful and stable enteric coated dosage form can be made without one or more separating layers.

It is submitted that referring to a possible embodiment as "optional" is not a disclosure or description of embodiments employing or failing to employ the "option". This is especially true where, as here, the specification contains no written description of such an embodiment, no enabling disclosure of how to make or use the "optional" embodiments and, not only fails to provide a best mode, but fails to disclose any mode.

A mere mention of a possible embodiment is not sufficiently definite or particular that, without undue experimentation, one of ordinary skill in the art can gain possession of the claimed subject matter based on the reference disclosure. See, *Sheppard*, supra. at page 45. Characterizing a feature as "optional" does not convey to one of ordinary skill in the art that the inventor had possession of that option or all other options. Accordingly, the Depui disclosure is not enabling to prepare stable and useful proton pump inhibitor oral dosage forms without having at least one separating layer. Hence there can be no anticipation.

During the June 10, 2003 telephone interview, the Examiners indicated that they were not maintaining that Depui disclosed a stable dosage form without a separating layer but only that one could follow the Depui examples and just omit the steps leading to the inclusion of the separating layer. Such literalism undermines the requirement that a reference contain an enabling disclosure.

Since Depui never exemplifies an embodiment without a supporting layer, there is no reasonable basis in the record to believe such an embodiment would be successful. See, *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988). Accordingly, the Examiner is called upon to comply with the provisions of 37 C.F.R. 1.104(d)(2).

Claims 15 to 25, 30 to 34, 36, 39 and 40 were rejected under 35 U.S.C. 102(e) as anticipated by Depui. It is submitted this rejection is also improper as a matter of law and should be withdrawn.

The Examiner's statement of rejection for these claims is exactly the same as that for the first group of claims except the Examiner now refers to Example 4 stating that "the examples utilize Wurster-type fluidized apparatus to coat the active agent onto the sugar core, followed by enteric coating".

Applicants repeat the above stated comments with respect to this rejection also. Further, Example 4 refers to an embodiment wherein a subcoating layer was applied to the core underneath the enteric coating layer. It also refers to an embodiment where other active ingredients (such as naproxen are included in the formulation. There is no mention of Wurster-type fluid bed or any conditions of operation. Accordingly, this rejection is also in error as a matter of law.

Claims 1 to 13 and 15 to 40 have been rejected under 35 U.S.C. 103(a) as patentable over Depui in view of comments set forth in the Official Action on pages 5 to 7. After discussing the disclosure of Depui the Examiner concludes that one of ordinary skill in the art would have been motivated to make an oral composition comprising an inert core, an active coating, and an enteric coating without the presence of a separating layer based on the reference and the expected result would be a successful composition for the treatment of gastrointestinal disorders. However, the Examiner never sets forth what criteria or what basis there is to believe that the resulting composition would be "successful". Applicants have submitted extensive material showing that one would have expected to the contrary. That is to say that in the absence of the separating layer, the composition would not be expected to be "successful" (whatever is meant by that term as employed by the Examiner). To the contrary, based on the submissions, one would have expected failure.

This is because as discussed above, Depui does not contain a single example that prepares such a composition and contains no information as to how such a composition would actually perform and relevant art teaches that the supporting layer is necessary. Curiously, Depui does not even include stability information in the formulations of the 14 examples. The request for compliance with 37 C.F.R. 1.104(d)(2) is repeated.

Applicants submit there is a sufficient side by side showing of record by the comparison of Depui's examples with the examples of '505 patent.

Applicants have previously submitted a chart comparing example 9 of Depui with Examples 7, 8 and Comparative Example V of the '505 patent. A comparison of the method to produce magnesium omeprazole pellets of Example 9 of Depui and the method to produce the pellets of Examples 7 and 8 of the '505 show that the **processes are identical** in those references. See previously submitted ***Annex 2***. (Amendment of June 26, 2003).

The core material of Depui's Example 9 has the same ingredients as the core material of Example 7 ('505 patent), the only difference being the ratio of magnesium omeprazole versus diluents, which is higher in Example 9. In both cases the core material is covered with hydroxypropylmethylcellulose ("HPMC") and the percentage of the polymeric film forming material used in the separating layer is essentially the same (11 and 10% respectively).

Finally, pellets having a separating layer are further coated with an enteric polymer and the ratios of that polymer used in the enteric layers in both examples are essentially the same (11 and 10%, respectively). In order to calculate the % of methacrylic acid copolymer, one can assume that the material used is 100g of a 30% aqueous suspension of the polymer. The formulation of Example 8 of the '505 patent is the same formulation of Example 7, wherein part of the mannitol diluent has been substituted by magnesium hydroxide.

As stated in column 13, lines 40 to 65 of the '505 patent, the formulation of the Comparative Example V is the same as in Example 8 but no subcoating layer is used and the pellets are prepared as described in Example 2 of the '505 patent.

Annex 3 of the June 2003 Amendment is a chart comparing Example 14 of the Depui with Examples 2, 3, 4 and Comparative Examples I, II and III of the '505 patent.

Example 14 of Depui shows an omeprazole formulation identical in respect to the core material to those of Examples 2, 3, and substantially similar to that of Example 4, of the '505 patent. In the latter example, sodium lauryl sulphate has been replaced by a different but also well known surfactant, Pluronic F 68. In Depui Example 14, the core material is further coated with a film coating polymer (hydroxypropylcellulose) used in a ratio of 8% whereas in Examples 2, 3 and 4 ('505 patent), the film forming coating polymer (HPMC or polyvinylpyrrolidone) is used in a 4 or 6% ratio.

Finally, in all the above cases, pellets with a separating layer are further coated with an enteric polymer used in an 8-10% ratio.

Again, the method to prepare omeprazole formulations of Example 14 Depui and of Examples 2, 3 and 4 of the '505 patent is the same.

The formulations of Comparative Examples I, II and II are identical or substantially similar to those of Examples 2, 3 or 4 ('505 patent) but lack the separating layer.

Table 5 (column 14, lines 18 to 41) of the '505 patent lists various parameters such as acid resistance and storage stability of the Examples 2 to 8 preparations (formulations with separating layer) and of the Comparative Example I-V (formulations without separating layer). This comparison shows stability problems or unacceptable low resistance to dissolution in acid media of the formulations lacking the separating layer, whereas the preparations with a separating layer have good gastric juice resistance and stability (see column 14, lines 64-68 and column 15 lines 1 to 31 of the '505 patent).

All example pellets of Depui have a separating layer. Some of Depui's examples are identical or substantially similar to the preparations of the '505 patent. The '505 patent contains a side by side comparison of preparations with and without a separating layer and shows that those lacking separating layer have problems. The Depui patent fails to inform as how to avoid the stability and acid resistance problems of the

formulations lacking separating layers and therefore, one of skill in the art would not be encouraged, or expect from Depui in view of the '505 patent to prepare a stable formulation lacking a separating layer.

Therefore, the stability difference in the Depui formulation where the drug dosage form is prepared with and without a separating layer has already been established by the '505 patent which is of record

During the June 10, 2003 telephone interview, Applicants' undersigned counsel discussed using the above comparison to show that the disclosure of the Depui was insufficient and that one of ordinary skill in the art could not, based on the Depui reference, achieve a stable product. It is submitted that the above showing is sufficient. See *In re Fouche*, 169 U.S.P.Q. 429, 433 (CCPA 1971).

The above comparisons were again discussed with the Examiner during the November 6, 2003 telephone interview. The Examiner inquired why the now claimed dosage form does not degrade as does Comparative Example III of the Lovgren Patent ("the '505 patent"). She also stated that she did not see a difference between the dosage form described in the Lovgren '505 patent or the Depui reference, and the now claimed invention.

The now claimed dosage form without a separation layer between the active containing layer and the enteric coating is stable because the active layer is homogeneous and non-porous. See pending claims 1, 34 and 36. The active containing layer is non-porous and since all the coating steps are performed in a single fluidized bed coater of the Wurster-type or the like.

This feature has been disclosed in the originally stated specification.

Page 2, lines 12-19 of specification reads as follows:

> *Numerous techniques recently have been developed for preparing systems of release in the form of microgranules wherein the mixture of active ingredient and excipients is submitted to a process of kneading, extrusion, spheronization, coating, etc. Each of these pelletization techniques calls for a different technology, so that there are many types of pelletization equipment, coating pans or drums, fluid-bed equipment, extruders-spheronizers and centrifuging equipment, among others. The final result would appear to be the same, although there are in fact considerable differences between the pellets made using each technique.* (underlining added)

Page 7, lines 1-5, states:

> *In the present invention a formulation and a working methodology in a fluid bed of the "Wurster" type or the like have been developed. In it, the negative factors which affected the methods described to date are eliminated and substantial changes introduced with respect to the methods of previous patents for pellets containing benzimidazoles.*

Page 8, lines 15-17, points out that:

> *The new galenical formulations object of the present invention are characterized in that they are spherical granules with a homogeneous active charge layer and a very unporous surface, formed by coating of an inert nucleus by spraying a single aqueous or hydroalcoholic mixture containing the active ingredient (anti-ulcer compound) together with the other excipients.*

Page 9, lines 19 to 21, reads as follows:

> *When a single suspension-solution is projected onto the inert nucleus, a less porous and more homogeneous product is obtained than in the procedures known to date, and all the subsequent operations are simplified considerably.* (Underlining added)

Also, on page 22 lines 1-2 and page 25, lines 13-14, it is disclosed that Photographs 4 and 8 show the low porosity and homogeneity of the coatings and the lack of pores accounts for the enhanced physical stability of the pellet.

Since the process is conducted in a single "Wurster" type fluidized bed coater, the claimed process need not encompass using other pieces of equipment different from fluidized bed coaters of the Wurster-type or the like.

Neither Lovgren nor Depui teaches the substantially spherical, stable oral formulation claimed of the present invention having a non-porous, homogeneous, active layer, or how to produce them, or a process whereby such a product is obtained.

Neither Lovgren nor Depui teaches that the homogeneous, nonporous characteristics and substantially spherical shape of the granules comprising an inert core and active coating layer are result effective parameters which influence the stability of benzimidazole containing pellets.

Lovgren and Depui disclose preparation of pellets wherein the benzimidazole core material are made by extrusion/spheronization (see Examples 2 to 8 and Comparative Examples I to V of Lovgren and Examples 9 and 14 of Depui). Extrusion spheronisation is a multi-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheroniser to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution.

Lovgren teaches that these extrusion/spheronization benzimidazole containing cores having a separating layer beneath the enteric coating, have good resistance to gastric juice as well as good stability whereas the same formulation lacking a separating layer (those of Comparative Examples I to V) experience at least one of stability problems or poor resistance to dissolution in acid media.

Depui also discloses the preparation of pellets by the powder-layering technique using a centrifugal fluidized coating granulator. See Depui Example 10. These pellets have a separating layer between the core material and the enteric coating.

An example of benzimidazole containing core prepared by powder-layering technique using a centrifugal fluidized coating granulator with enteric coating layer but lacking the separating layer is disclosed in Example 6 of Takeda's EP 642797 ("Takeda '797"):

Example 6

Production of a formulation comprising lansoprazole and a gastrointestinal mucosa-adherent solid preparation containing AMOX

1) Granules containing lansoprazole was prepared as follows.

Ingredients	mg
Lansoprazole	30
Magnesium Carbonate USP	22.4
Sugar Spheres NF	110.0
Sucrose NF	59.8
Starch NF	36.4
Low-Substituted Hydroxypropyl Cellulose NF (L-HPC-31)	40.0
Hydroxypropyl Cellulose NF (HPC-L)	1.4
Methacrylic Acid Copolymer LD (Eudragit L30D-55) (Röhm Pharma Co.)	44.6
Polyethylene Glycol NF (PEG-6000)	4.4
Titanium Dioxide USP	4.4
Polysorbate 80 NF (Rheodol TW-0120)	2.0
Talc USP	14.0
Colloidal Silicon Dioxide NF (Aerosil)	0.6
Purified water * USP	q.s.
Total	370.0

*: Removed during the manufacturing process
USP: The United States Pharmacopeia
NF: The National Formulary

Sugar spheres was coated with a mixture of lansoprazole, magnesium carbonate, sucrose, starch and L-HPC-31 by means of spraying aqueous HPC-L solution in a centrifugal fluid-bed granulator (CF-1000S, Freund Co.), and the resultant wet granules were dried in a vacuum oven at about 40°C for about 18 hours, and then sieved. The obtained granules were coated with aqueous enteric Eudragit suspension containing PEG-6000, talc, titanium dioxide and Rheodol TW-0120 in a fluid-bed coater (F10-Coater FLO-60, Freund Co.), and sieved, and then dried in a vacuum oven at about 42°C for about 18 hours. The obtained granules were mixed with talc and Aerosil.

2) 370 mg of granules containing lansoprazole as obtained in 1) above and 100 mg of gastrointestinal mucosa-adherent solid preparation containing AMOX as obtained in Reference Example 3 were packed in No.0 capsules to yield a capsule preparation.

The previously submitted Declaration by Dr. Molina, Mr. Picornell and Mr. Bravo ("the Picornell Declration") sets forth the attempts to reproduce Example 6 of Takeda '797. This experimental work led to

the following conclusion:

> *"Therefore, even after correcting the defect of the procedure described in section 1) of example 6 of European Patent Application EP 0 642 797 in relation to the quantity of binder material, this procedure does not yield enteric-coated gastroresistant granules of lansoprazole that are appropriate and acceptable from the pharmaceutical standpoint. Consequently, the use of the above procedure does not yield granules equal or similar to those obtained with the procedure contemplated in Patent Application PCT WO 99/06032, particularly as described in example 1 therein."*

Therefore, when enteric-coated gastroresistant benzimidazole granules are made by powder-layering technique using a centrifugal fluidized coating granulator without a separating layer between the active layer and the enteric coating, it results in granules having stability problems and unacceptable low resistance to gastric fluid. See Paragraph No. 5 of the Picornell Declaration.

This kind of powder-layering process is carried out in a centrifugal bead granulator, shown below schematically:

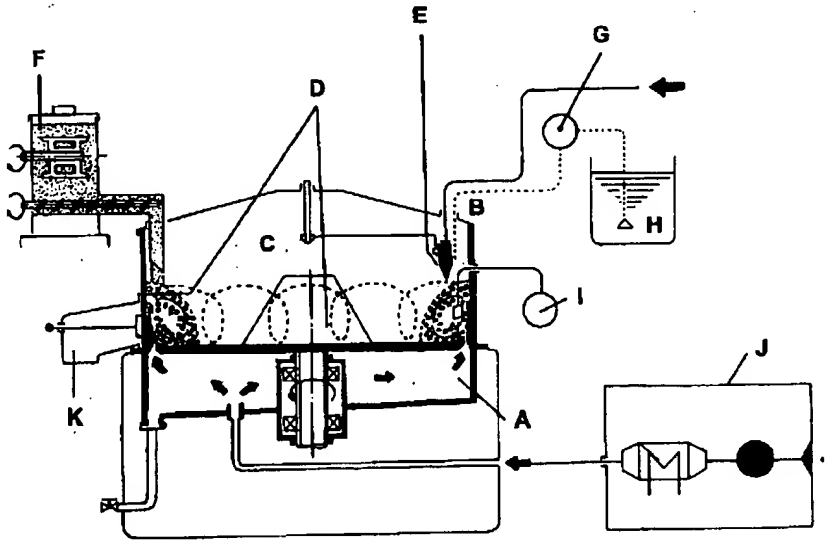


Figure 2. Schematic diagram of the centrifugal granulator. Key: Inlet air (A), Outlet air (B), Granulation chamber (C), Rotor (D), Solution spray system (E), Powder feeder (F), Liquid pump (G), Liquid vessel on a balance (H), Moisture sensor (I), Blow air generator system (J) and Product outlet (K) (modified from Goodhart 1989).

See the previously submitted selected pages of an Academic dissertation on "Centrifugal granulation process for preparing drug-layered pellets based on microcrystalline cellulose beads", held at the University of Helsinki on April 2001. The complete text of the dissertation can be downloaded from:

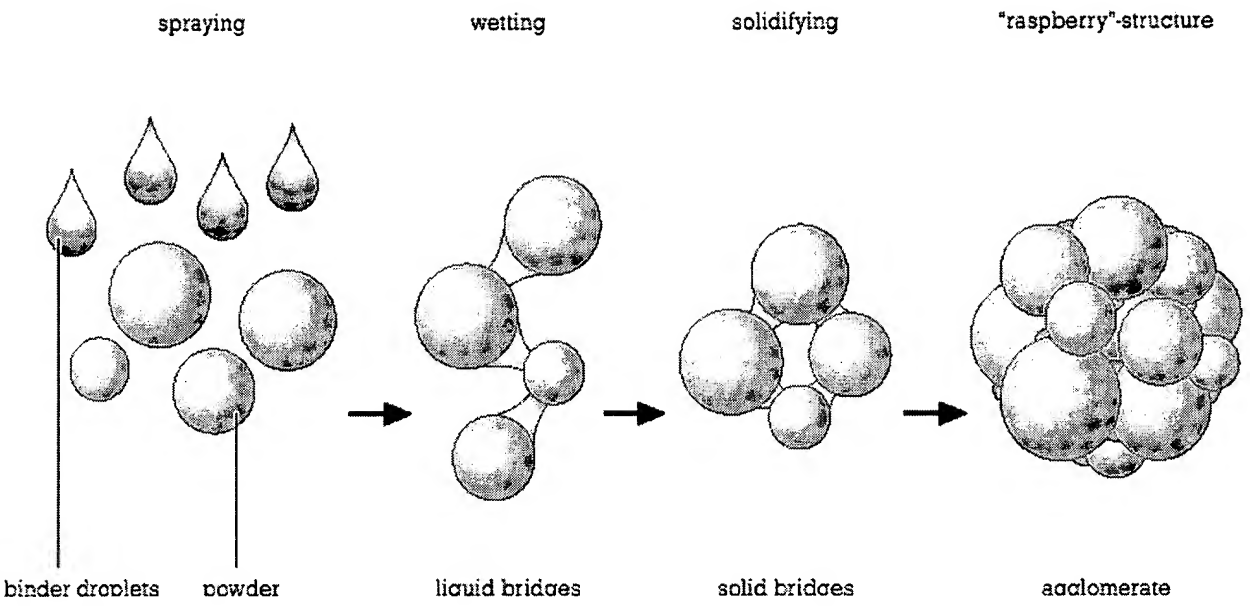
http://ethesis.helsinki.fi/julkaisut/mat/farma/vk/rashid/centrifu.pdf

The schematic depicts a laboratory scale centrifugal fluid-bed granulator Freund CF-360EX, Freund Industrial Co., similar to the centrifugal fluid-bed granulator CF-1000S Freund Co. used in the Example 6 of Takeda '797.

As can be observed in the schematic, the beads are placed in a granulation chamber provided with a rotating plate at the bottom. The rotating plate centrifugally displaces the granules towards the chamber-wall, while the air flows by the plate edge. Simultaneously, the powder mixture is dosed from a powder feeder and the binding solution from a liquid vessel, producing a granulation process.

According to Takeda '797 Example 6, the granules after drying in an oven, are provided with an enteric coating by a subsequent coating process carried out in a fluidized-bed coater.

Applicant has already submitted technical trials which prove that by using the above process it is not possible to obtain pharmaceutically acceptable two-layered pellets , and this may very well be due to the structure of the resulting active coated pellets having a "raspberry" type structure, that is a porous, non-compact, non-homogeneous, open surface.



However, in the present invention the inert nuclei are coated with a single solution-suspension containing the active ingredient, the binder and the other excipients of the first active containing layer, by using a single fluidized-bed coater.

As disclosed in the present application appropriate fluidized-bed coaters are, for example, those of Wurster-type or similar. In the Wurster process, the inert nuclei to be coated are fluidized in an upward-moving airstream. A high-velocity airstream is introduced into the fluidized bed, causing a spout. A draft-tube partition is placed around the spout to prevent the beads in the spout from colliding with the particles descending in the fluidized bed. A cyclical flow of particles is thus created. When beads enter the high-velocity spout, they are uniformly accelerated and physically separated from each other. As the high-velocity air and the beads move up, the solution-suspension for coating is applied by a spray nozzle mounted at the base of the spout. The process air that moves the beads also serves to dry the coating. Because of the large amounts of air used, excellent drying is obtained. When the airstream and particles clear the top of the partition, the air in the spout spreads out to fill the expansion chamber, and the beads settle out on the top of the bed of fluidized beads. Because the bed of particles is fluidized by air, additional

drying occurs as the beads descend to the bottom of the bed and re-enter the partition, where they are accelerated again by the high-velocity airstream and receive additional coating.

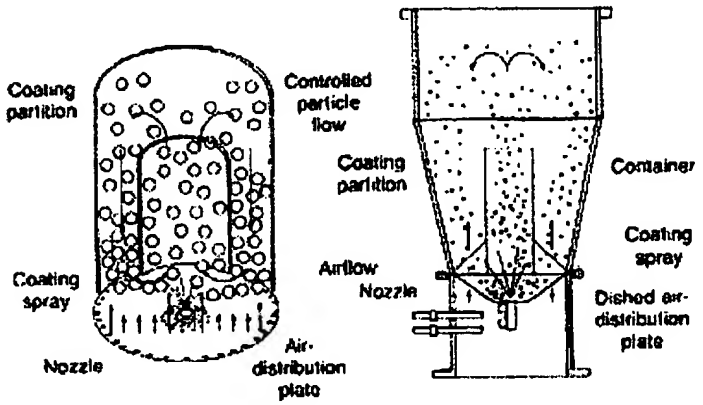


Figure 7: A standard Wurster chamber with a flat bottom plate and a container with a dished air-distributor plate.

See Attachment 2. "Airflow in batch fluid-bed processing", downloaded from:

http://www.niroinc.com/html/pharma/pairflowarticle.html

at the web page of Niro Inc., the manufacturer of the Wurster-type fluidized-bed coater used in Examples 1 and 2 of the present application.

After the coating with the active layer, the enteric coating is applied to the pellets in the same fluidized-bed coater.

Accordingly, the product and process of the present application does not encompass the extrusion/spheronization technique nor the powder layering process, because it does not refer to a granulation process for agglomerating different kind of solids in particulate or powdered form, but to a pure coating process with a single coating homogeneous solution-suspension. Thus, the pellets obtained are different in structure and properties from the pellets or the core material according to the other processes.

The structure of the pellets of the present invention accounts for the compactness, non-porosity, homogeneity, closed surface of the particles and, as a consequence of that, its stability.

Depui Examples 1, 3, 4, 5 and 11, refer to the formation of pellets by suspension layering in a fluid bed apparatus but it is clear from the specification (col. 9, ll. 57 *et. seq.*) that Depui sees no relationship between any particular layering technique or conditions and the stability or gastric resistance of the resulting product.

An objective achieved by the present invention is a more simple and efficient process to obtain two-layered benzimidazole anti-ulcer pellets in form of substantially spherical granules provided with a homogeneous non-porous active charge layer and an outer enteric layer, which are uniform and well shaped, having good friability and which are stable for an acceptable time period. See the present specification at pages 20, 24 and 25.

The solution proposed consists of coating the inert nuclei with a single solution-suspension containing the active ingredient, the binder and the other excipients of the first layer and, after drying, providing the obtained pellets with a second enteric layer, the coating operations being performed in a single Wurster-type or similar fluidized-bed coater.

As explained in the first page of the present application there are many techniques to prepare microgranules and multi-layered pellets and there are also many types of pelletization equipment.

Since neither Lovgren nor Depui teaches that the stability of pellets containing benzimidazoles could depend on the homogeneous, nonporous characteristics and spherical shape of the granules comprising benzimidazole and that enteric coated benzimidazole containing granules lacking a separating layer or the coating technique and both patents fail to recognize that granules made either by extrusion/spheronization or by powder layering techniques have stability problems and/or unacceptable low resistance to gastric fluid, one of ordinary skill in the art would not be motivated to prepare stable two-layered benzimidazole anti-ulcer pellets by selecting a suspension layering method using a "fluid bed apparatus" as generically disclosed in examples 1, 3, 4, 5 and 11 of the '771 patent.

Without an inventive effort the skilled person would not be motivated to use the claimed process or have any reasonable expectation of success.

As indicated on page 1 of Attachment 2 to the December 12, 2003 Amendment After Final Rejection, significant amounts of solid material are processed using fluid-bed technology and one primary factor influencing a fluidized-bed process is airflow. Figure 1 of Attachment 2 shows the typical components of a fluid-bed processing unit. A fluid bed is a bed of solid particles with a stream of air or gas passing upwards through the particles at a rate great enough to set them in motion. Different types of bed are formed depending upon the movement of bubbles through the bed. See for instance, Example 3 of Attachment 2.

There are many kinds of fluidized bed apparatus. On page 4 of Attachment 3 (document downloaded from http://www.glatt-weimar.de/download/konti_ws_en.pdf) (December 12, 2003), there is an example of a fluid bed useful for building up particles from powder-agglomeration or for liquid-granulation and to coat particles. All these processes can be accomplished by selecting air with different velocities in different chambers, selecting air temperatures and by the correct placement of the nozzles in the fluid bed.

None of the examples of the '771 discloses the use of a Wurster-type or the like fluidized bed coater. The selection of this type of fluid bed equipment allows strict and automated control of the spraying and drying conditions necessary to apply the two layers to the inert core.

Claim 35 has been rejected under 35 U.S.C. 103(a) as unpatentable over Depui in view U.S. Patent No. 4,853,230 to Lovgren et al. ("Lovgren '230"). It is submitted this rejection is also improper and should be withdrawn.

Lovgren '230 contains claims which were obvious in view of the claims of Lovgren '505. The disclosure of each of the '505 and '230 patents were substantially identical. It is submitted applicant's comments above with respect to Lovgren '505 are equally applicable to Lovgren '230.

The Lovgren reference teaches the necessity of the separating layer. Therefore, to combine this reference with Depui is improper since a vital and important part of the Lovgren reference would have to be disregarded. Clearly, the Examiner is engaging in a pick and choose technique to formulate an obviousness rejection based on hindsight reconstruction. This is improper under 35 U.S.C. §103. Also see *In re Ratti* 123 U.S.P.Q. 349 (CCPA, 1959).

That Lovgren may suggest a single active ingredient does not remedy the deficiencies of Depui.

Claims 15 to 25, 31, to 34, 36, 39 and 40 have been rejected under 35 U.S.C. 103(a) as unpatentable over Depui in view of U.S. Patent No. 4,017,647 to Ohno et al. ("Ohno") or U.S. Patent No. 2,799,241 to Wurster. It is submitted these rejections are improper and should be withdrawn.

Depui has been discussed above. The Examiner cites Ohno apparently for providing an enteric coating on a solid dosage form. The rejection seizes on a phrase from column 3, lines 24-40 taken out of context from the Ohno reference.

The objective of the Ohno disclosure is to enteric coat a dosage form with an aqueous solution of a polymeric substance having carboxyl groups in the water soluble salt form and contacting the coated dosage form with an inorganic acid to covert the polymer substance into the water insoluble acid form. The citation of Ohno highlights that the prior art did not appreciate the significance of the procedure by which the active layer is applied.

The Examiner states that Wurster teaches that the Wurster-type fluidized apparatus provides for a uniform coating preventing a coating material from sticking to the inner surface of the chamber. From these isolated disclosures, the Examiner comes to a conclusion of obvious.

Applicants have never denied that a Wurster-type fluidized apparatus is known. However, what is not disclosed or suggested in any of the references is that by utilizing this type of apparatus, one can obtain a substantially non-porous soluble active layer which can eliminate the need for a separating layer in those types of formulations where the prior art required the presence of the separating layer to protect the active ingredient

from the deleterious affects of enteric coatings. None of the cited art provides disclosures of this feature or a suggestion of such a feature or how to obtain it.

Claims 1 to 13, 26 to 29, 37 and 38 have been rejected under 35 U.S.C. 103(a) as unpatentable over Depui. It is submitted this rejection is also improper and should be withdrawn.

The Examiner's rejection is largely a repeat of the prior rejections based on the Depui reference. Accordingly, Applicant refers to the prior comments regarding this reference.

The Examiner's response to the previously submitted arguments gives the impression that she may have misconstrued or misunderstood Applicants' argument. Applicants do not contest that Depui discloses the need for an enteric coating. It is obvious that Depui has an enteric coating layer. Applicants' position is that although Depui refers to a separating layer (that layer between the active ingredient and the enteric coatings) as "optional", there is no disclosure as to how to obtain a stable formulation without the use of the separating layer.

The Examiner's quotes from the Webster dictionary do not remedy Depui's deficiencies. True, Depui used the word "optional". However, the mere use of a word does not in and of itself mean that an undescribed embodiment is enabled. If that were the case, an applicant could use many words in a specification without enabling those embodiments and thus preclude subsequent applicants from obtaining patent protection on improvements which were never enabled by the original disclosure. While Depui may indicate that separating layers are not essential for the invention, Depui does not to disclose how to obtain a stable formulation without a separating layer.

The Examiner argues that a patent disclosure is not limited to an example or to a preferred embodiment. While that may be true, that does not permit an applicant to broadly refer to an invention but fail to contain enabling disclosure commensurate in scope. This is especially true where, in prior art owned by the same assignee, the necessity for a separating layer has been shown. See Applicants' above discussion of the Lovgren '505 patent.

The phrase "consisting essentially of" is interpreted in light of the specification. It is clear, that in the present invention, and from the claim language, that the phrase "consisting essentially of" should not be interpreted to permit an applied separating layer. Under the Examiner's reasoning, use of phrases such as "consisting essentially of" would render the cited limitations meaningless because each positive limitation would have to be accompanied by a comprehensive list of exclusions from that limitation. Such is not the way a claim should be interpreted or even could be interpreted in practice.

The Examiner appears to be of the opinion that because she has cited a reference for only one specific purpose that that is the only purpose or basis for which that reference can be considered. This is in direct violation of 35 U.S.C. 103 that states the art is to be considered as a whole. Applicant have set forth in significant detail the teachings of the Lovgren reference. As indicated above, in Example 1 of the Lovgren '505 patent contains a comparative showing which illustrates that those formulations without a separating layer do not have sufficient stability with respect to the proton pump inhibitors. This is information which is in the prior art and which is of record in this case and which must be fully considered whether the Examiner has relied on that part of the Lovgren '505 reference or not. See, *In re Piasecki and Meyers*, 223 U.S.P.Q. 785, 788 (Fed. Cir. 1984).

The question here is not whether the secondary reference should be removed. The issue, which the Examiner has never addressed throughout this prosecution, is that Lovgren '505 teaches the necessity of a separating layer. The language of Depui which merely refers to the separating layer as "optional" but which fails to disclose an embodiment where no separating layer is present, is undermined by the teachings of the prior art. Thus, Lovgren whether combined with Depui for purposes of the '103 rejection or, whether submitted by Applicants to establish the lack of enablement by Depui, is a reference of record and must be considered.

The Examiner's comments with respect to the Lovgren formulation are not understood. If the Examiner is indicating that the 103 rejection based on Depui does not permit Applicants to rely on Lovgren to show that the art teaches away from the claimed invention, this is a direct violation of the command of 35

U.S.C. 103 that the art be considered as a whole. If the Examiner is referring to the rejection based on Depui under 35 U.S.C. 102, Lovgren is submitted to show that Depui lacks enablement.

At the top of page 15 the Examiner indicates the question of stability is one degree. While in a broad sense such a statement may be true, the point here is that to obtain a pharmaceutical dosage form, one must meet certain stability requirements. Claims 38 to 40 recite that the dosage form is stable. Further, the specification contains sufficient information to show the minimum stability requirements. The Examiner states that such features are not recited in the claim. However, such features need not be recited in a claim. See, *Preemption Devices, Inc. v. Minnesota Mining and Manufacturing Company*, 221 U.S.P.Q. 841, 844 (Fed. Cir., 1989).

The Examiner states that the Wurster-type fluidize bed limitations are only recited in the process claims not the product claims and she therefore concludes that the argument is moot. However, the Examiner has rejected the process claims on the same art, applied in the same manner, as applied to the product claims. Further, the Examiner is impermissibly reading disclosure into the Depui reference, disclosure which is not there and which the Examiner should not be attempting to rely on. The Examiner is thus rewriting the specification of the reference. That is impermissible.

The Examiner's conclusion that it is obvious for one of ordinary skill in the art to manipulate conditions to obtain the best possible results is not understood. The Examiner fails to identify which parameters she is referring to or where the prior art predicted that such undefined parameters could be manipulated or what would be expected. If the prior art does not predict or identify parameters as result effective, there is no motivation to manipulate those parameters. See, *In re Sebek*, 175 U.S.P.Q. 93 (CCPA, 1972).

In view of the foregoing, reconsideration and allowance of the application with claims 1 to 13 and 15 to 40 are earnestly solicited.

It is believed that no fees or charges are required at this time in connection with the present application; however, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By _____
Vincent M. Fazzari
Reg. No. 26,879
551 Fifth Avenue, Suite 1210
New York, New York 10176
(212) 687-2770

Dated: December 1, 2004